

72A SUB B16  
ID NO: 1 in an amount effective to inhibit hyperproliferation of a tumor cell having high *Nr-CAM* expression.

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A12 SUB B17  
3. (Amended) A method of inhibiting cell overproliferation in a subject comprising administering to a tumor in a subject in which such treatment or prevention is desired an effective amount of a *Nr-CAM* antisense nucleic acid comprising at least 15 nucleotides that inhibits *Nr-CAM* function, wherein the *Nr-CAM* antisense nucleic acid is hybridizable in a cell to at least a portion of a RNA transcript of the *Nr-CAM* gene of SEQ. ID. NO.: 1.

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Please add the following claim:

A13 SUB B20  
22. (New) The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises a liquid carrier.

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REMARKS

Claims 1-21 have been examined in the instant application. Claims 2, 14, 15, 18, 20, and 21 have been withdrawn from consideration pursuant to 37 C.F.R. § 1.142(b) as being directed to a non-elected invention. Applicants reserve the right to prosecute the subject matter of the non-elected claims in a related, co-pending application. By this amendment claims 10 through 12, 13, 16, 17, and 19 have been canceled without prejudice to Applicants' right to prosecute the subject matter of these claims in a related, co-pending application. The claims have been canceled in order to further expedite prosecution of certain claimed aspects of the invention. The application has also been amended to add dependent claim 22, which recites a particular embodiment of claim 1. Support for this new claim can be found throughout the specification and in particular on, for example, page 87, lines 23-27, and page 88, lines 18-32. Further, claims 1 and 3 have been amended to set forth the invention with greater particularity as described in detail below. All of the amendments presented herein are fully supported by

the specification and no new matter has been added to the application. Entry of this amendment is respectfully requested.

Rejections under 35 U.S.C §112, Second Paragraph:

Claims 10 and 16 stand rejected under 35 U.S.C. § 112, second paragraph, the Examiner believing the claims to be indefinite since they claim subject matter not elected in the present invention. The Examiner notes, for example, that limitations specifying *Nr-CAM* antibodies are not embraced within the elected group, *i.e.*, *Nr-CAM* antisense molecules and methods of using such antisense molecules.

Applicants, while not acquiescing to the Examiner's rejection or reasons for the rejection note that claims 10 and 16 have been canceled in order to further expedite prosecution of certain aspects of the present invention as set forth in detail below. Therefore the rejection of the claims under 35 U.S.C. § 112, second paragraph is mooted.

Rejections under 35 USC § 112, First Paragraph:

Claims 1, 3-13, 17, and 19 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner believing that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. In particular, the Examiner believes that the specification does not reasonably provide enablement for “any inhibitory molecule to any *Nr-CAM* from any species nor any method of use of such molecules in any whole organism for therapeutic purposes as broadly claimed.” The Examiner asserts that the lack of correlation for the breadth of the claims stems from the fact that there is a “high level of unpredictability” regarding antisense technology for “therapeutic, *in vivo* applications.” The Examiner believes that various factors contribute to the asserted unpredictability of the art, including (1) stability of any *Nr-CAM* antisense molecules *in vivo*; (2) effective delivery to the whole organism and specificity to the

target tissues by routes of administration other than direct injection into the tumor; (3) dosage and toxicity of antisense molecules administered by any other route of administration than direct injection; and (4) entry of antisense molecules in the cell and effective action therein. Further, the Examiner alleges that factors constituting barriers to successful delivery to the organism include penetration of the plasma membrane, withstanding enzymatic degradation, and non-specific binding.

As an initial matter, Applicants respectfully disagree with the Examiner's overview of the specification as filed. The Examiner has suggested that the only antisense molecules that have been enabled by the specification are those disclosed in the examples (*i.e.*, pCMV1/3Nr-AS and pCMV2/3Nr-AS) and only for direct administration to mice glioblastomas. On the contrary, the specification as filed provides a description of methods to produce antisense molecules other than the specific examples as well as methods for their administration to species other than mice and for the inhibition of various tumors having high *Nr-CAM* expression. *See, e.g.*, pages 75-79, 83-89, and 104-107 of the specification and throughout the description of the specific embodiments wherein methods are generally provided for making antisense molecules with *in vitro* and *in vivo* inhibitory activity against hyperproliferative cells and tumors not limited to glioblastoma cells nor limited to mice.

Specifically, beginning at page 74, line 20 of the specification, the use of antisense nucleic acids for the regulation of *Nr-CAM* expression is described. Various methods for the synthesis of antisense nucleic acids and nucleic acid derivatives are described at pages 75-79. Methods for testing a particular antisense nucleic acid in a cell, *i.e.*, a tumor cell isolated from a partial, is disclosed, for example, at pages 81-83 of the specification. Various delivery systems for antisense nucleic acids are provided, at for example, pages 83-90, and can include encapsulation on liposomes, microparticles, microcapsules, recombinant cells, recombinant retroviruses, and the like. Particular examples of antisense nucleic acids are disclosed in the present application and include pCMV-1/2 Nr-AS and pCMV-2/3 Nr-AS as well as phosphorothiosate oligonucleotides H-1, H-2 and H-3 (SEQ ID NOs.: 22, 23 and 24, respectively).

Applicants also respectfully disagree with the Examiner's view of the art as it relates to the disclosed methods. The Examiner believes that the art demonstrates that one of skill in the art would conclude there was unpredictability in regard to antisense molecules for therapeutic, *in vivo* applications. First, as a general matter, Applicants note that, at the time of filing of the instant application, there had been demonstrated and recognized success in the art of various antisense molecules used *in vivo*, including use in therapeutic applications. *See generally, e.g.,* Flanagan, *Cancer Metastasis Rev.* 17:169-76, 1998; (reviewing clinical development of five antisense oligonucleotides for treatment of solid tumors and non-Hodgkin's lymphoma and stating that, as a "new class of drugs," antisense technology "has nearly reached maturity and will have an important role in the treatment of cancer and other human diseases") attached for the convenience of the Examiner. *See also* Ho and Hartwig, *Curr. Opin. Mol. Ther.* 1:336-43, 1999 (reviewing applications of antisense oligonucleotides in the study of protein function in the CNS) attached hereto.

Further, Applicants respectfully note that the scope of enablement need "only bear a '*reasonable correlation*' to the scope of the claims." MPEP § 2164.08 at 2100-186 (emphasis added), *citing In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Accordingly, everything necessary to practice the invention need not be disclosed, MPEP § 2164.08 at 2100-186. Rather, "all that is necessary is that one skilled in the art be able to practice the invention, *given the level of knowledge and skill in the art.*" *Id* (emphasis added). Moreover, the presence of inoperative embodiments within the scope of a claim does not render a claim non-enabled where the skilled artisan "could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with the expenditure of no more effort than is normally required in the art." MPEP § 2164.08(b) at 2100-188, *citing Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984).

In view of these standards, Applicants respectfully disagree with the Examiner's reliance on Flanagan *et al.*, (*Nat. Biotechnol.* 17:48-52, 1999) regarding the penetrability of antisense oligonucleotides into target cells and enzymatic degradation of

such antisense molecules. Applicants note that, at the time of filing of the instant application, various methods were known in the art that address the issues of cellular uptake and stability of oligonucleotides *in vivo*, resulting in increased resistance to degradation as well as increased penetration into cells. *See, e.g.*, page 76, line 2 through page 77, line 23 of the specification as filed, and as an additional example attached hereto Schwab *et al.*, *Ann. Oncol.* 5 Suppl. 4:55-8, 1994 (greater intracellular stability through association with polyalkylcyanoacrylate nanoparticles).

Applicants also respectfully remind the Examiner that, to the extent that Flanagan *et al.* address the feasibility of self-permeable oligonucleotides, *inoperable embodiments are not encompassed by a claim* where no undue experimentation is required to assess such operability. MPEP § 2164.08(b) at 2100-188; *Application of Angstadt*, 190 USPQ 214, 218 (CCPA 1976) (holding that, even in an unpredictable art, 35 U.S.C. § 112 does *not* require “disclosure of a test with every species covered by a claim”). In this case, at the time of filing, the operability of oligonucleotides not linked or associated with permeabilizing agents could be assessed without undue experimentation using techniques known in the art, including, *e.g.*, fluorescent labeling of the oligonucleotides such as, *e.g.*, the labeling performed in Flanagan *et al.* to assess cell permeability. Such methods, moreover, would allow the skilled artisan to determine, without undue experimentation, which modes of administration facilitate accessibility of the antisense oligonucleotides to target tissues or organs. Also, based on Flanagan *et al.*, the skilled artisan would likely not select methods using antisense nucleic acids in a formulation that did not include additional elements to enhance cell membrane permeability and reduce stability. Such as the use of direct injection and retroviral vectors specifically disclosed in the examples of the present application.

Further, Applicants note that, assuming, *arguendo*, the presence of non-specific effects or distribution of *Nr-CAM* antisense molecules to non-target tissues, the claims are *not* rendered nonenabled under 35 U.S.C. § 112 by such factors. The claims do not recite any limitation regarding the presence or absence of effects, whether specific or non-specific, other than the inhibition or treatment of “*tumorigenesis*” or other disease

involving “*overproliferation*.” “Side effects” (*i.e.*, effects of a pharmaceutical composition other than the desired endpoint) are routinely tolerated in the clinic and are rarely, if ever, completely absent. Moreover, given the nature of clinical studies and the reasonable expectations of time and other resources typically needed for determining appropriate dosing of a pharmaceutical composition, such determination of dosage and toxicity is a routine part of clinical development and, therefore, not undue.

Applicants also respectfully disagree with the Examiner’s reliance on Branch (*TIBS* 23:45-50, 1998) regarding the specificity of antisense oligonucleotides. The Examiner alleges that “*in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success” and that “discovery of antisense molecules with ‘enhanced specificity’ *in vivo* requires further experimentation for which no guidance is taught in the specification.” Applicants initially note that Branch only addresses the specificity of antisense molecules in the intracellular environment and does not explicitly address issues relating to efficacy *in vivo* in whole organisms (note that discussions in Branch relating to “*in vivo*” efficacy refer to antisense molecules in cultured cells, *see, e.g.*, page 49 and Figure 3 of the specification).

In this regard, Applicants believe that, at the time of filing of the instant specification, the skilled artisan would be able to distinguish, without undue experimentation and using methods known in the art, those *Nr-CAM* antisense molecules that have the desired specificity inside cells from those that do not. First, Applicants note that, while Branch, as cited by the Examiner, states that “effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells,” Branch does *not* state that such empirical methods cannot reliably determine effective antisense molecules from a given set of candidates. Although Branch asserts that such methods are time-consuming, the time and expense required to execute an experiment, standing alone, do not show undue experimentation. *See United States v. Teletronics, Inc.*, 8 USPQ2d 1217, 1224 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989); MPEP § 2164.06 at 2100-182. Nor do such factors, *a priori*, speak to the predictability of success. Indeed, Branch states that “effective antisense molecules are

typically selected from 20-50 candidates.” (See page 49, second column.) In addition, methods in the art are known for efficiently screening large numbers of such molecules: methods are known for automated production of oligonucleotides (*see, e.g.*, specification, page 77, lines 23-32 of the specification as filed) as well as for large-scale cell-based screening assays (*e.g.*, automated systems in 96- or 384-well formats).

Second, while Branch states that, inside cells, it is “not possible to improve specificity by raising the temperature or changing the ionic conditions,” the skilled artisan would recognize that antisense candidates for intracellular hybridization can be evaluated before screening on cells: (1) methods for determining complementary nucleic acid sequences that will exhibit specific hybridization based on length and G + C content under particular hybridization conditions are known in the art (*see, e.g.*, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press 1989), and (2) the skilled artisan would recognize that *in vitro* hybridization temperature and ionic conditions could be manipulated to mimic cellular temperature and ionic content.

Also, Applicants note that other methods were known in the art at the time of filing that would allow the artisan to efficiently and reasonably predict, through *in vitro* methods, those antisense oligonucleotides that are efficient for *in vivo* antisense targeting. *See* Matveeva *et al.*, *Nucleic Acids Res.* 25:5010-16, 1997 (A rapid *in vitro* method for obtaining RNA accessibility patterns for complementary DNA probes: correlation with an intracellular pattern and known RNA structures) attached hereto. Therefore, Applicants believe that the specification is enabling for *Nr-CAM* antisense molecules as presently claimed.

The Examiner also alleges that the results regarding the administration of “specific antisense” in the specification “do not correlate to antisense to any region of any species of *Nr-CAM* for any routes of administration.” To the extent that the Examiner refers only to the working examples presented in the specification, Applicants respectfully note that working examples are only one factor in determining enablement, *see* MPEP § 2164.02 at 2100-176. Further, Applicants again respectfully remind the

Examiner that the scope of enablement in the specification need bear only a *reasonable* correlation to the scope of the claims and that this inquiry is conducted in view of the knowledge of the skilled artisan. *Id.* § 2164.08 at 2100-186.

In view of these standards, Applicants first respectfully refer the Examiner to the discussion above relating to the determination of antisense oligonucleotides with intracellular specificity, which Applicants believe has already addressed the issue of determining, without undue experimentation, the operability of antisense molecules to any particular region of *Nr-CAM*. Also, Applicants again note that the specification provides methods for making and using antisense molecules to *Nr-CAM* not limited to any species or mode of administration. (*See, e.g.*, pages 75-79 and 83-89 of the specification.) Applicants note that, because *Nr-CAM* genes had been cloned from several species, including human, mouse, rat, and chicken, and because these *Nr-CAM* gene sequences show more than 80% homology (*see* page 6, lines 30 and 31 of the specification), the skilled artisan would reasonably expect an *Nr-CAM* gene to be present in a given species and, based on the high degree of homology, would be able to clone the *Nr-CAM* gene without undue experimentation. Various methods were also known in the art that address cellular uptake and stability of oligonucleotides *in vivo*, the skilled artisan would reasonably expect that operable modes of administration other than direct administration to a tumor would be successful and that such modes of administration can be determined without undue experimentation in applicable animal models. Applicants note that, at the time of filing, modes of administration other than direct administration to a tumor were known in the art. *See, e.g.*, Flanagan, *Cancer Metastasis Rev.* 17:169-76, 1998 (citing earlier references showing that phosphorothioate oligonucleotides administered intravenously to murine tumor xenograft, transplant, and inflammation models “have demonstrated potent and specific antisense inhibition without the need of any delivery reagent”); Holmlund *et al.*, *Curr. Opin. Mol. Ther.* 1:372-85, 1999 (reviewing earlier references showing efficacy of human anticancer antisense molecules using intravenous administration as well as murine antisense molecules using intravenous and intraperitoneal administration). Therefore, Applicants believe that the claims as filed



are sufficiently enabled under § 112 for regions and species of *Nr-CAM* and modes of administration in addition to those presented in the examples.

Although Applicants disagree with the Examiner's rejection as set forth above and believe the invention as originally claimed is fully described and enabled, but in order to further expedite prosecution of the application and without acquiescing, claims 1 and 3 have been amended as follows.

Claim 1 has been amended to clarify that the *Nr-CAM* antisense nucleic acid is "hybridizable in a cell" to at least a portion of the RNA transcript of the *Nr-CAM* gene of SEQ ID NO.: 1. Because Applicants believe that this amendment merely clarifies what would be known to the artisan regarding specificity of *Nr-CAM* antisense molecules, Applicants believe that this amendment is not narrowing. Support for this amendment is found in the specification on, for example, page 81, lines 5-22 of the specification.

Claim 3 has also been amended to expedite prosecution of a certain cell overproliferation aspect of the invention. Claim 3 now recites that the method is for inhibiting or tumorigenesis and that the *Nr-CAM* antisense nucleic acid comprises at least 15 nucleotides and "is hybridizable to at least a portion of a RNA transcript of the *Nr-CAM* gene of SEQ. ID. NO.: 1." Support for these amendments is found in the specification at, for example, page 75, lines 22-32, page 99, lines 21-26, page 81, lines 5-22 and Figure 2A.

In light of the above amendments and remarks, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 3-13, 17 and 19 under 35 U.S.C. § 112, first paragraph.

#### Rejections under 35 USC §102

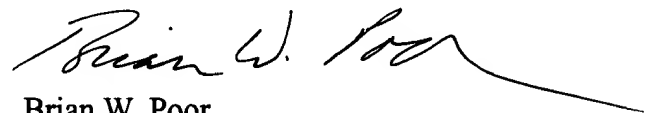
Claim 16 stands rejected under 35 USC §102(b) as being anticipated by Moscoso *et al.* (*J. Comp. Neurol.* 352:321-34, 1995). In view of cancellation of claim 16, for reasons set forth in the Remarks above and without prejudice to Applicants' right to

prosecute the subject matter of this claim in a related, co-pending application, Applicants respectfully note that this rejection is mooted.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



Brian W. Poor  
Reg. No. 32,928

Dated: 23 May 2002

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

Please delete the pages designated "-i-" through "-v-" comprising the Table of Contents.

At page 4 please delete the paragraph beginning at line 22 and replace with the following:

Several CAM family members are implicated in the process of tumorigenesis including, N-CAM, CEA, ([Cacinoembryonic] Carcinoembryonic Antigen), DCC (Deleted in Colon Carcinoma) and L1.

At page 22 please delete the paragraph beginning at line 13 and replace with the following:

*Nr-CAM* is a gene identified by the method of the invention, that is expressed at high levels in glioblastoma multiforme tissue as well as certain other[s] forms of tumors and cancers.

At page 24 please delete the paragraph beginning at line 23 and replace with the following:

The present invention relates to a novel role of *Nr-CAM* in the promotion of cell transformation and tumorigenesis. In particular, the present invention relates to the Applicants' findings that (a) *Nr-CAM* is highly over-expressed in glioblastoma multiforme tumor tissue and is over-expressed in a number of other primary tumors; and (b) over-expression of *Nr-CAM* in the anti-sense orientation results in decreased cellular proliferation and colony formation of glioblastoma cells in soft agar.

At page 35, please delete the portion of the paragraph beginning at line 15 and replace with the following:

The identified and isolated gene can then be inserted into an appropriate cloning vector. A large number of vector-host systems known in the art may be used. Possible vectors include, but are not limited to, plasmids or modified viruses, but the vector system must be compatible with the host cell used. Such vectors include, but are not limited to, bacteriophages such as lambda derivatives, or plasmids such as p[P]BR322 or pUC plasmid derivatives or the Bluescript vector (Stratagene). The insertion into a cloning vector can, for example, be accomplished by ligating the DNA fragment into a cloning vector, which has complementary cohesive termini. However, if the complementary restriction sites used to fragment the DNA are not present in the cloning vector, the ends of the DNA molecules may be enzymatically modified. Alternatively, any site desired may be produced by ligating nucleotide sequences (linkers) onto the DNA termini; these ligated linkers may comprise specific chemically synthesized oligonucleotides encoding restriction endonuclease recognition sequences. In an alternative method, the cleaved vector and *Nr-CAM* gene may be modified by homopolymeric tailing. Recombinant molecules can be introduced into host cells via transformation, transfection, infection, electroporation, *etc.*, so that many copies of the gene sequence are generated.

At page 105, please delete the paragraph beginning at line 20 and insert the following:

As shown in Figures 8 [(A and )B,] (A and B), *hNr-CAM* was expressed at high levels in melanoma G361, lymphoblastic leukemia (MOLT-4) and Burkitt's lymphoma Raji cell lines. A low level of *hNr-CAM* expression was observed in promyelocytic leukemia (HL-60), HeLa cell S3, chronic myelogenous leukemia (K-562), colorectal [adrenocarcinoma] adenocarcinoma (SW480) and lung carcinoma (A549). All of the cell lines studied herein expressed *hNr-CAM* mRNAs that are 1.4 kb as compared to the 7.5 kb transcript expressed in normal brain (Figure 5 (A and B)). HeLa cells S3

express low levels of both transcripts. Melanoma G361 express high levels of the 7.5 kb and low levels of the 1.4 kb transcript, suggesting alternative splicing of *hNr-CAM* mRNA during tumorigenesis.

At page 109, please delete the paragraph beginning at line 6 and insert the following:

To obtain antisense "*Nr-CAM* 1/3 clone", *Nr-CAM* 1/3 (corresponding to nucleotides beginning at nucleotide 119 and ending at nucleotide 1434 of Figure 2A) was amplified using primers BT306 (5' TAGATACAAGTAGTCTAATGCAGCTTAAAATA ATGCC 3')(SEQ. ID. No.: 18) and BT307 (5' AGATAGATCCGCGGATATCCATATT CATTAGAGGCATTG 3') (SEQ. ID. No.: 19) (see Figure 2A) and cloned into precut pCMVneo vector cut with [SACII] SacII and [SPEI] SpeI restriction enzymes. PCR amplification was carried out for 1 cycle at 94°C 3 min, 61°C 1 min, 72°C 4 min, then for 30 cycles at 94°C 1 min, 61°C 1 min, 72°C 4 min followed by 1 cycle at 94°C 1 min, 61°C 1 min, 72°C 10 min. The PCR product was cut with [SpeI] SpeI and [ScaII] SacII and cloned in the antisense direction into the pCMVneo vector precut with SacII and SpeI enzymes. Orientation of the *hNr-CAM* gene was confirmed by restriction digestion of specific enzymes. This clone was termed "pCMV-1/3Nr-AS".

At page 122, please delete the paragraph beginning at line 25 and insert the following:

The effect of ODNs on inhibition of *hNr-CAM* expression can be evaluated using the methodology described previously (Anfossi, *et al.*, 1989 *Proc Natl Acad Sci USA*, 86:3379-3383). Briefly, 5GB, HTB-16 and GB1690 cells are plated per well in 96-well plates in media without ODNs. Twenty-four hours later, the culture [is] media is changed to contain a final concentration of 1mmole/L, 3mmole/L, or 10mmole/L ODNs. Control cultures received fresh culture media without ODNs. After 4-5 days post-transfection, cell proliferation is analyzed using a cell proliferation assay kit from Promega (Madison, WI). Expression is analyzed using immunocytochemistry

methods, described previously (Sehgal, *et al.*, 1998, *Int. J. Cancer*, 76(4):451-458).

These oligonucleotides are [be] tagged with fluorescent tags to ensure their entry into the cells.

At page 124, please delete the paragraph beginning at line 11 and insert the following:

As a non-limiting, illustrative [exmmple] example the following is presented. A Retro-X™ system is used to deliver and over-express antisense *hNr-CAM* gene in glioblastoma cells. Retro-X™ system is a complete retroviral gene expression system that can transduce up to 100% of cells. Together with the [RetroPack™] RetroPack™, PT67 cell line, the Retro-X Vectors produce infectious, replication-incompetent retrovirus that can be used to introduce a gene of interest into a wide variety of mammalian cell types *in vitro* or *in [vivoy] vivo*. The highly efficient transduction machinery of retroviruses can stably integrate the cloned gene into the host genome of nearly all mitotically dividing cells. A retroviral vector containing the gene of interest (*hNr-CAM*) is first transfected into the packaging cell line. Antibiotic selection can then be used to obtain a population of cells that satably expresses the integrated vector and, if desired, high-titer clones can be isolated from this population. Virus produced by either stably transfected cells can be used to infect target cells.

At page 126, please delete the paragraph beginning at line 13 and insert the following:

Northern blot analysis for the expression of *hNr-CAM*. Cell clones that are expressing low level of *hNr-CAM* are expanded in culture. Approximately  $1 \times 10^7$  glioblastoma cells (1690-CRL, 1620-CRL, HTB-16, C6, 9L gliosarcoma) will be injected subcutaneously into the flanks of ten female athymic nude mice (two sites each). Tumor growth [vill] will be analyzed every week for at least fourteen weeks and compared between anti-sense *hNr-CAM* and mock infected glioma cell lines.